All-trans retinoic acid enhances bystander effect of suicide-gene therapy against medulloblastomas.

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Abstract

In our previous study we evaluated the antitumor effect of herpes simplex virus-thymidine kinase gene (HSV-tk) on human medulloblastomas (MBs) in a therapeutic delivery system using the immortalized neural stem cell (NSC) line C17.2. However, our findings indicated that the bystander effect between C17.2tk and Daoy MB cells was weak compared to the bystander effect between NSCtk and C6 glioma cells. Gap junction intercellular communication (GJIC) is the main mechanism mediating the bystander effect in HSV-tk gene therapy. All-trans retinoic acid (ATRA) has been shown to up-regulate the expression of Connexin43 and GJIC. In this study we investigated the synergistic effect of ATRA and HSV-tk gene therapy in the treatment of MBs. We found that the expression of Connexin43 in Daoy cells was significantly increased when cells were exposed to 3µmol/l of ATRA (P<0.05). After co-culturing C17.2tk cells with Daoy cells at different ratios ranging from 1:1 to 1:16, ATRA significantly increased the bystander anti-tumor effect compared to ATRA-untreated cells (P<0.05). In intracranial co-implantation experiments, mice co-implanted with C17.2tk/Daoy cells and treated with a combination of ATRA and GCV had significantly smaller tumors compared to the animals treated with GCV alone (P<0.05). Together, our results show that ATRA enhanced the tumoricidal effect in HSVtk/GCV suicide gene therapy against Daoy MB cells by strengthening the bystander effect in vitro and in vivo.

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PMID: 21872643 [PubMed - as supplied by publisher]